REMARKS

Claims 127-137 are currently pending. Claims 1-126 were previously cancelled.

Rejections under 35 U.S.C. § 103(a)

Claims 127-133, 136 and 137 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Cubicciotti *et al.* (U.S. Patent No. 6,287,765).

Applicants respectfully disagree.

According to *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398, 82 U.S.P.Q.2d 1385 (2007) and M.P.E.P. § 2141, the framework for the objective analysis for determining obviousness under 35 U.S.C. § 103 is stated in *Graham v. John Deere Co.*, 383 U.S. 1, 148 U.S.P.Q. 459 (1966). Obviousness is a question of law that is based upon underlying factual inquiries. The factual inquiries enunciated by the Court are as follows:

1) determining the scope and content of the prior art;

2) ascertaining the differences between the claimed invention and the prior art; and

3) resolving the level of ordinary skill in the pertinent art.

Objective evidence relevant to the issue of obviousness, if present, must also be evaluated. Such evidence, sometimes referred to as "secondary considerations", may include evidence of commercial success, long-felt but unsolved needs, failure of others and unexpected results.

The claimed invention is not obvious in view of the cited reference.

The Claimed Invention

Independent claim 127 recites a method comprising the steps: providing a target and a target partner that do not bind to each other in the absence of an aptamer regulator; contacting a

mixture of nucleic acids with the target and the target partner under conditions that disfavor efficient binding between the target and the target partner; partitioning nucleic acids bound to a target-target partner complex from unbound nucleic acids; and retaining the nucleic acids bound to the target-target partner complex, thereby identifying an aptamer regulator that binds to a target wherein binding of the aptamer regulator to the target increases the binding affinity of the target for the target partner relative to the affinity of the target for the target partner when the target is not bound by the aptamer regulator such that binding of the aptamer regulator to the target is a prerequisite for target-target partner complex formation.

Scope and Content of the Cited Art

Cubicciotti *et al.* ("Cubicciotti") discloses multi-molecular devices and drug delivery systems prepared from synthetic heteropolymers, and methods for selecting single synthetic nucleotides, shape-specific probes and specifically attractive surfaces for use in these multi-molecular devices. Specifically, Cubicciotti describes nucleotide-based and non-nucleotide multi-molecular structures and multi-molecular devices capable of positioning at least two specific recognition pairs within close spatial proximity. That is, selected molecules can be conjugated to defined positions of nucleotide or non-nucleotide scaffolds to enable both controlled intermolecular positioning and functional coupling of molecules. As a result, properties and products are achieved by template-directed assembly of cooperative pairs and groups of molecules. Therefore, Cubicciotti relates to methods and structures for coupling the activities of two or more molecules or groups of molecules to perform functions dependent upon the spatial proximity of the constituent molecules. Cubicciotti also discloses a method for screening and selecting diverse nucleotide libraries for functional coupling between a donor and an acceptor species.

Differences Between the Claimed Invention and the Cited Art

Independent claim 127, and the claims that depend therefrom, is directed to a method for identifying an aptamer regulator that binds to a target, wherein binding of the aptamer regulator to the target increases the binding affinity of the target for a target partner relative to the affinity of the target for the target partner when the target is not bound by the aptamer regulator. Independent claim 127 also recites that the target and the target partner do not bind to each other in the absence of an aptamer regulator, and that binding of the aptamer regulator to the target is a prerequisite for target-target partner complex formation. Therefore, the binding of the aptamer regulator to the target **enables** the binding of the target to the target partner.

The examiner states that Cubicciotti discloses methods "which include selection from a highly diverse nucleic acid library (meets the limitation in claim 129), isolation (including the steps of "partitioning" and "retaining" in claim 127c and 127d), characterization, and sequencing of individual selected nucleotides as well as screening (meets the limitation in claim 137) for a defined sequence segment capable of binding a complex comprising two molecules (col. 162, lines 63-67)."

Applicants disagree. In fact, Applicants do not understand how the examiner can make the above statements regarding method steps when Cubicciotti does not disclose any of the steps in Applicants' claimed method.

Even if, as the examiner states, the Cubicciotti method can be used to identify a defined sequence segment capable of binding a complex comprising two molecules, that is not Applicants' invention. As stated previously, Applicants' invention is a method for identifying an aptamer regulator that binds to a target, wherein binding of the aptamer regulator to the target enables the binding of the target for a target partner. On the other hand, the defined sequence

segment in Cubicciotti binds to a complex of two molecules. That is, the defined sequence segment binds to a pre-existing complex of two molecules. If the defined sequence segment were to function as an aptamer regulator, then binding of the defined sequence segment to one of the molecules would enable binding of such molecule to the other molecule. The two molecules in Cubicciotti are able to bind to each other in the absence of the defined sequence segment, which is contrary to Applicants' claimed method.

The examiner also states that "[a]lthough Cubicciotti does not explicitly disclose that the target and target partner do not bind to each other in the absence of an aptamer (claim 127a limitation) and that the conditions disfavor binding between the target and the target partner (claim 127b limitation), Cubicciotti clearly suggests combining the selection of a first aptamer binding to a first nonoligonucleotide molecule, which can be the claimed target, and the selection of a second aptamer binding to a second nonoligonucleotide molecule, which can be the claimed target partner, for the purpose of assembing the two molecules in close distance for coupling function".

Applicants agree with the first part of the examiner's statement that Cubicciotti does not disclose: 1) that the target and target partner do not bind to each other in the absence of an aptamer, and 2) that the conditions disfavor binding between the target and the target partner.

Assuming, arguendo, that the second part of the examiner's statement is true, that is not Applicants' invention. Applicants' invention is a method for identifying a single aptamer, *i.e.*, an aptamer regulator, that binds to a target so that the target can then bind to a target partner. On the other hand, Cubicciotti discloses two defined sequence segments, wherein each defined sequence segment binds to a separate target, and then attaching the two defined sequence segments either directly or indirectly to bring both targets in close spatial proximity. In addition,

the aptamer regulator of Applicants' invention enables the target to bind to the target partner. On the other hand, Cubicciotti couples two defined sequence segments in order to bring two targets together that normally interact, such as a ligand and its receptor, or a target and its receptor.

In addition, the examiner states that it is immediately apparent to one skilled in the art that the synthetic heteropolymer of Cubicciotti would meet the limitation of an aptamer regulator that binds to a target and a target partner under conditions disfavoring binding between the target and target partner.

Applicants disagree with the examiner's statement for several reasons. First, Applicants do not understand how it would be immediately apparent when, by the examiner's own admission, Cubicciotti does not disclose that the target and target partner do not bind to each other in the absence of an aptamer, and that the conditions disfavor binding between the target and the target partner. Second, the synthetic heteropolymer of Cubicciotti comprises two defined sequence segments, wherein each defined sequence segment is bound to a separate target, and the two defined sequence segments are attached either directly or indirectly to bring both targets in close spatial proximity. If a defined sequence segment were to function as an aptamer regulator, then binding of the defined sequence segment to a target would enable binding of such target to another target. As a result, the synthetic heteropolymer of Cubicciotti does not meet the limitations of an aptamer regulator.

The examiner further states that it would be obvious to one skilled in the art at the time of the invention to select for a synthetic heteropolymer, such as the claimed aptamer regulator, from a diverse pool of nucleic acids comprising a first aptamer that recognizes a target and a second aptamer that recognizes a target partner, under conditions that the target and target partner do not bind to each other in the absence of an aptamer regulator, with the predictable results of the

aptamer regulator binding to both the target and target partner to form a multi-molecular complex.

Applicants disagree. For the reasons stated above, the synthetic homopolymer of Cubicciotti is not an aptamer regulator. The synthetic heteropolymer of Cubicciotti comprises two defined sequence segments, wherein each defined sequence segment is bound to a separate target, and the two defined sequence segments are attached either directly or indirectly to bring both targets in close spatial proximity. As stated previously, both targets in the Cubiciotti method normally interact, such as a ligand and its receptor, or a target and its receptor. In addition, an aptamer regulator does not bind to both the target and the target partner to form a multi-molecular complex. An aptamer regulator binds to a target such that binding of the aptamer regulator to the target enables the binding of the target for a target partner. That is, the target and the target partner do not bind to each other in the absence of an aptamer regulator.

Cubicciotti is only concerned with bringing two molecules into close spatial proximity in order to simulate the productivity and efficiency of biological systems. In fact, Column 10, lines 36-49 of Cubicciotti state:

> This invention is not specifically drawn to the properties of the template material, itself, but to the wealth of useful devices that can be assembled by combining selected molecules within a single multimolecular structure. A central inventive step of this disclosure is demonstration of the variety of different devices that can be prepared by either 1) tethering two members of at least one specific binding or shape-specific recognition pair to a common molecular scaffold, so the recognition partners may exist in either of two states (e.g., specifically bound or dissociated) or 2) combining at least two different specific recognition pairs within a single multimolecular structure, i.e., a pair of specific recognition pairs, each pair having two members.

The purpose of the Cubicciotti method differs from that of the claimed method. Hence, the methods differ, which is apparent because each of the methods contains different steps.

Level of Ordinary Skill in the Pertinent Art

Applicants submit that a person having ordinary skill in the art would be a college educated scientist. Such a person would have the capability of understanding the scientific principles applicable to the pertinent art.

Summary

Applicants submit that after analyzing the cited reference and the claimed invention in view of the *Graham* factors, the cited reference does not render obvious the claimed invention. Accordingly, withdrawal of this rejection under 35 U.S.C. § 103(a) is respectfully requested.

Claim 135 stands rejected under 35 U.S.C. § 103(a) as being unpatentable over Cubicciotti *et al.* (U.S. Patent No. 6,287,765) in view of Gallivan (U.S. Patent Publication No. 2003/0064931).

Applicants respectfully disagree.

The Claimed Invention

Dependent claim 135 recites that the retained nucleic acids from the target-target partner complex are removed by contacting the bound nucleic acids with excess free target.

Scope and Content of the Cited Art

The Cubicciotti reference was discussed above in response to the previous rejection.

Gallivan ("Gallivan") discloses nucleic acid constructs, and systems and methods for the control of gene expression in cells and for the detection of target molecules in cells; methods to identify nucleic acids encoding polypeptides or ribonucleic acids involved in the biosynthesis, degradation or other modification of a target molecule; methods to generate a cell-based biosensor for a target molecule; and cells that are dependent on a target molecule for growth or

viability, and the use of such cells in the selection of enzymes having desirable catalytic activities.

Differences Between the Claimed Invention and the Cited Art

Applicants agree with the examiner that Cubicciotti does not disclose eluting nucleic acids with excess free target.

Gallivan discloses that, during SELEX, RNAs that bind to a target molecule column may be eluted with excess of the target molecule. On the other hand, Gallivan does not disclose that such an elution step could be used in another method, such as the claimed method.

This rejection only relates to a dependent claim. For the reasons stated above and for the reasons stated in response to the previous rejection, Gallivan, when combined with the teachings of Cubicciotti, does not cure the deficiencies of Cubicciotti.

Level of Ordinary Skill in the Pertinent Art

Applicants submit that a person having ordinary skill in the art would be a college educated scientist. Such a person would have the capability of understanding the scientific principles applicable to the pertinent art.

Summary

Applicants submit that after analyzing the cited references and the claimed invention in view of the *Graham* factors, the cited references do not render obvious the claimed invention. Accordingly, withdrawal of this rejection under 35 U.S.C. § 103(a) is respectfully requested.

Claim 134 stands rejected under 35 U.S.C. § 103(a) as being unpatentable over Cubicciotti *et al.* (U.S. Patent No. 6,287,765) in view of Gold *et al.* (U.S. Patent No. 5,763,173).

Applicants respectfully disagree.

The Claimed Invention

Dependent claim 134 recites that the retained nucleic acids from the target-target partner complex are removed by eluting the nucleic acids with an agonist competitor to the target.

Scope and Content of the Cited Art

The Cubicciotti reference was discussed above in response to the first rejection.

Gold *et al.* ("Gold") disclose methods for identifying aptamers to thermostable DNA polymerases. More specifically, Gold discloses aptamers that are capable of binding to the Taq and Tth thermostable DNA polymerases, thereby inhibiting their ability to catalyze the synthesis of DNA at ambient temperatures. This is useful in polymerase chain reaction (PCR) because the presence of the aptamers in the PCR mixture prevents the thermostable DNA polymerase from amplifying background DNA by preventing any DNA synthesis at lowered temperatures prior to or during the cycling reaction.

Differences Between the Claimed Invention and the Cited Art

Applicants agree with the examiner that Cubicciotti does not disclose eluting nucleic acids with an agonist competitor to a target.

The examiner states that Gold discloses the specific procedure of eluting bound DNA aptamers with a target competitor, tRNA, to the target polymerase (column 9, lines 15-26).

Applicants disagree.

Column 9, lines 15-26 of Gold recite:

> Once equilibrated at room temperature, the DNA was incubated for 15 minutes with the appropriate target polymerase in the presence of 2 nmoles of tRNA as a

> competitor. After incubating, hSA was added to the reaction mixture to a final concentration of 0.01%. Polymerase-DNA complexes were separated from unbound DNA by nitrocellulose filtration through a prewet nitrocellulose filter (0.45 μM) under suction. The filter was immediately washed with 20 mL of the binding buffer, 20 mL of 0.5 M urea in the binding buffer, and 0.5 M urea in water. Bound DNA was isolated from the filters by elution and precipitation from ethanol in the presence of carrier tRNA (5 μg).

This passage is taken from Example 1 of Gold. Example 1 describes the experimental procedures used in the selection of aptamers to both the Taq and Tth polymerases. It is clear from the last sentence of this passage that tRNA is not used to elute the bound DNA, but is used to precipitate the DNA. tRNA is commonly used in ethanol precipitation to recover small amounts of DNA by making the pellet visible.

The examiner also states that tRNA is a target competitor of DNA to the DNA polymerase. Applicants disagree. tRNA is not a competitor of DNA in binding to a DNA polymerase because DNA polymerases do not specifically bind to tRNA. tRNA binds to mRNA and to individual amino acids. tRNA is used in the Gold method to block non-specific binding and to reduce background. Even if tRNA is a competitor, it is not an agonist competitor, as is required by the claims.

For the reasons stated above, Applicants disagree with the examiner's statement that it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the selection method disclosed by Cubicciotti so as to further include the step of eluting the nucleic acids with an agonist competitor to the target, as taught by the Gold patent, with a reasonable expectation of success because this elution technique is a routine procedure known in the art of aptamer selection.

Furthermore, this rejection only relates to a dependent claim. For the reasons stated above and for the reasons stated in response to the first rejection, Gold, when combined with the teachings of Cubicciotti, does not cure the deficiencies of Cubicciotti.

Level of Ordinary Skill in the Pertinent Art

Applicants submit that a person having ordinary skill in the art would be a college educated scientist. Such a person would have the capability of understanding the scientific principles applicable to the pertinent art.

Summary

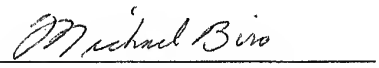
Applicants submit that after analyzing the cited references and the claimed invention in view of the *Graham* factors, the cited references do not render obvious the claimed invention. Accordingly, withdrawal of this rejection under 35 U.S.C. § 103(a) is respectfully requested.

CONCLUSION

Applicants submit that the claims are not obvious in view of the cited references. Accordingly, reconsideration of the rejections and allowance of the claims at an early date are earnestly solicited.

If there are any questions regarding this Response or if the undersigned can be of assistance in advancing the application to allowance, please contact the undersigned at the number set forth below.

Respectfully submitted,



Michael G. Biro, Reg. No. 46,556
Sr. Patent Attorney
Archemix Corp.
300 Third Street
Cambridge, MA 02142
Direct: (617) 475-2324
Main: (617) 621-7700
Fax: (617) 621-9300

Jennifer A. Karnakis, Reg. No. 53,097
Attorney for Applicants
c/o MINTZ, LEVIN
One Financial Center
Boston, MA 02111
Direct: (617) 348-1618
Main: (617) 542-6000
Fax: (617 542-2241
Customer No. 69262